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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/544,665	04/06/2000	Douglas Cines	9596-67U1	9220

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EXAMINER	
GUPTA, ANISH	
ART UNIT	**PAPER NUMBER**
1654	16

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Please find below and/or attached an Office communication concerning this application or proceeding.

16

Office Action Summary	Application No.	Applicant(s)	
	09/544,665	CINES ET AL.	
	Examiner	Art Unit	
	Anish Gupta	1654	

-- The MAILING DATE of this communication appears on th cov r sh et with the correspond nce address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-24* is/are pending in the application.

4a) Of the above claim(s) *11-16 and 21-24* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-10 and 17-20* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *15* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claim Rejections - 35 USC § 112

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 5-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention for the reasons set forth in the previous office action and the reasons set forth below.

Applicants argue that "the claims of the invention are to be read in the light of the specification." Then Applicants point to the specification in different aspects of biological activity.

Applicant's arguments filed 10-16-02 have been fully considered but they are not persuasive.

The MPEP states "'reading a claim in light of the specification, to thereby interpret limitations explicitly recited in the claim, is a quite different thing from reading limitations of the Specification into a claim, to thereby narrow the scope of the claim by implicitly adding disclosed limitations which have no express basis in the claim.'" Here, references made by Applicant to PAI-1 dependent cell adhesion, disease states, and abnormal cell migrations have no express basis in the claim. In essence, Applicants are attempting to import subject matter from the specification into the claims. This is impermissible. See MPEP 2111.

Rejection is maintained.

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make

and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 5-10 and 17-19 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the peptide EEIIMD and SGTVASSSTAVIVSARSAPEEIIMD for inhibiting PAI-1- dependent adhesion of a cell, does not reasonably provide enablement for any peptide comprising EEIIMD, beyond SGTVASSSTAVIVSARSAPEEIIMD, and affecting biological processes such as angiogenesis, organogenesis, ovulation, inflammation, cancer, tumor cell invasion and metastasis, and atherosclerosis. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to enable the invention commensurate in scope with these claims for the reasons set forth in the previous office action and the reasons set forth below.

The factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have been described in In re Wands, 8 USPQ2d 1400 (Fed. Cir. 1988). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary. When the above factors are weighed, it is the examiner's position that one skilled in the art could not practice the invention without undue experimentation.

Applicants argue that the test for enablement is whether any experimentation necessary is undue. Applicants state that Ngo et al. does not address prediction of structure of small peptides. Applicants state that the instant application provides guidance in experimental result and scientific reasons so that the correlation of structure sequence is not predictable. Further, the reference of

Rudinger, Applicants argue is more than 22 years old and the and "cannot be considered indicative of the stat of the art at the time of filing a rapidly advancing field."

With respect to the articles regarding the angiogenesis, Applicants state that the reference cited, Black et al, "characterizes the field of angiogenesis treatment as 'extremely hot', and states that four companies are conducting Phase 1 trials for angiogenesis inhibitors, and two are conducting Phase II trials. This degree of success does not suggest a field that is prohibitively unpredictable as researchers are indeed succeeding in developing treatment methodologies." Moreover, Applicants also make reference to the Mayo Clinic program for Phase I Director's statement that there is optimism about anti-angiogenesis treatments. Finally, Applicants state that issues such as method of administrations and dosage and who would take them "are all issues that can be resolved by routine experimentation, and do not amount to 'undue experimentation.'" Applicants conclude the specification has provided guidance as to the promotion of binding of scuPA to LM-TK-cells and promotion of fibrinolysis in mice. "Further, other assay to determine the efficacy of treatments on angiogenesis, organogenesis, ovulation, inflammation, cancer and tumor cells invasion and metastasis and atherosclerosis are well known in the art at the time of filing."

Applicant's arguments filed 10-16-02 have been fully considered but they are not persuasive.

First, there were some issues raised with regards to Ngo et al. and its pages. The pages relied upon from the reference were 492-495 which were included with the office action. However, since Applicants requested, the entire reference has been furnished for their convenience. It should be noted that this copy was obtained from a different source and the page numbers do not

correspond to the copy which Applicants have. Pages 492-495 corresponds to pages 65-69 in present copy.

With respect to this reference, Ngo et al., it does not make a distinction between a small peptide and large peptide. The claims of the instant Application allow the peptide to be up to 46 amino acids, while defining only five. It is well known in the art that a small peptide will also conform to a three-dimensional structure. Thus the conclusions set forth in Ngo et al. are equally applicable to small peptides and large peptides since both conform to a three-dimensional structure. Applicants state that the specification provides predicitbility for structure prediction but do not specify how. Reviewing the pages cited by Applicants, it is unclear how there is ample disclosure of experimental results and scientific reasoning so that the correlation of structure to sequence is not predictable. These pages only disclose two peptides that are both five amino acids in length. It is unclear how the three-dimensional structure of a 46 amino acid of formula one can be predicted from these two five-amino acids.

With respect to Rudinger et al., the mere fact that it is 22 years old does not take away from the conclusions. Applicants have not provided any reference to counter the conclusions set forth by this reference. If Applicants that the art of peptide chemistry has dramatically changed in the past 22 years and the significance of particular amino acids or sequences for different aspects of biological activity can be predicted a priori, the Applicants are requested to establish this via references' and/or declaration. Absent this, mere arguments about the age of the reference are not sufficient basis to conclude that this reference is not reflective of the state of the art as of the filing of the instant application.

As for the arguments regarding angiogenesis, Applicants rely on the fact that the this field is "exteremly hot" and that the Director of the Mayo Clinic program is optimistic about the anti-angiogenesis treatment. However, the mere fact that a field is hot and there is optimism is not sufficient basis for concluding that there would not be undue experimentation. The field of cancer treatment and anti-angiogenic treatments are fraught with problems of predicibility as indicated in the previous office action. To further bolster this argument, more references have been furnished to illustrate the state of the art. It is well known in the art that anti-angiogenic drugs, while effective in vitro and in mice, are not effective in humans. For example, Dermer states that "immunotherapy's killing power of the transformation of 3T3 cells by a mutated protooncogene, simply does not have the same significance for cells in vivo.' (See page 320). Further, "[t]he facts indicate, however, that petri dish cancer is really poor representation of malignancy, with characteristics profoundly different from human disease." (See page 320). Similar sentiments are echoed in a Science article by Trisha Gura. The article indicates that the fundamental problem in cancer research is that model systems are not predictive of in-vivo activity (see page 1041). The article goes on to state xenograft models in mice "don't behave like naturally occurring tumors in humans--they don't spread to other tissues." (See page 1041). Further, other systems such as clonogenic assays are not always helpful since they "can't always predict how a tumor will respond to a drug in an animal" and "[s]ometimes they don't work because the cells simply fail to divide n culture." (See page 1042). In essence, the art indicates that "rodents are better predictors of human reaction to cardiovascular or anti-inflammatory agents than cancer or diseases of the central nervous system." (See Time article by Frederic Golden on page 44). The instant specification provides guidance in the way of cell assay and animal models involving mice. However as stated

above, it is unclear of the prohibitive value that results obtained from these models with respect to humans. In the instant specification, Applicants have not even provided a single assay method to give insight as to assess the anti-angiogenic effects.

Further, Applicants state that dosage, methods of administrations, and who should take them can be determined by routine experimentation and do not amount to "undue experimentation." The MPEP states "it is not necessary to specify the dosage or method of use if it is known to one skilled in the art that such information could be obtained without undue experimentation. If one skilled in the art, based on knowledge of compounds having similar physiological or biological activity, would be able to discern an appropriate dosage or method of use without undue experimentation, this would be sufficient to satisfy 35 U.S.C. 112, first paragraph." Here, the art does not recognize the ability of similar peptides that have similar activity form which dosage could be ascertained. Applicants have not pointed to any such peptides. Further, even with optimism, Mayo Clinic states that many crucial questions need to be asked about potential anti-angiogenic agents such as: what are the appropriate regimens, methods of administrations and doses and who should take them and when since it has been speculated that pregnant women and people with healing wounds should avoid known anti-angiogenic drugs such as angiostatin or endostatin. Applicants' specification does not answer these "crucial questions" and thus one would be burdened with undue experimentation.

As stated in the previous office action, the specification is similar to the non-enabling disclosure of *Ex parte Sudilovsky*, 21 U.S.P.Q2d 1702 (BPAI 1991). The disclosure of the instant application, with regard to the biological activity, is confined to broad allegations and suggestions without substantiating working examples. Although working examples are not necessary in the

specification, lack of a working example, however, is a factor to be considered, especially in a case involving an unpredictable and undeveloped art. When a patent applicant chooses to forego exemplification and bases utility on broad terminology and general allegations, he runs the risk that unless one with ordinary skill in the art would accept the allegations as obviously valid and correct, the examiner may, properly, ask for evidence to substantiate them. *In re Novak*, 306 F.2d 924, 134 USPQ 335 (CCPA 1962) 4; *In re Fouche*, 439 F.2d 1237, 169 USPQ 429 (CCPA 1971). In this case, the disclosure has not provided evidence of record of a single compound that would affecting a biological process, such as angiogenesis, organogenesis, ovulation, inflammation, cancer, tumor cell invasion and metastasis, and atherosclerosis.

Rejection is maintained.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 1, 5-6, 8, 10, 17 remain rejected under 35 U.S.C. 102(b) as being anticipated by Pannekoek for the reasons set forth in the previous office action and the reasons set forth below.

The claims are drawn to a peptide comprising the sequence EEIIMD and methods of using said peptides.

Applicants argue that the reference does not teach the sequence as claimed in the rejected claims. The sequence of SGTVASSSTAVIVSARSAEEIIMD is mutated and is replaced by another sequence. Thus, the refernce does not anticipate the claimd method.

Applicant's arguments filed 10-16-02 have been fully considered but they are not persuasive.

On page 5 of the reference, PAI-1 is defined to of the sequence SGTVASSSTAVIVSARMAPEEIIMD (see page 5, lines 23-27). On page 13 of the reference the data shows that PAI-1 inhibited thrombin in the presence and absence of vitronectin. (see page 13, lines 5-20, see also results in figure 2). This sequence anticipates the claimed invention since X1 correspond to the 19 amino acid peptide SGTVASSSTAVIVSARSAP, contains the sequence EEIIMD, and X8 would be a hydrogen due to the carboxyl terminal of Aspartic Acid. Thus, the peptide anticipates the claimed invention.

New Grounds For Rejections

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

5. Claims 7, 9, 18-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pannekoek as applied to claim 1, 5-6, 8, 10, 17 above.

The reference of Pannekoek has been discussed supra. The difference between the reference and the instant application is that the reference does not specifically teach the administration of the peptdie to humans.

However, PAI-1 mutant analogs can be adminstered intravenously to be used as a thrombolytic agent (see page 5, lines 10-15). Though the reference does state that the mutants posses some better activity than the native sequence, the reference demonstrates that the native sequence is effective a a thrombin inhibitor in the presence or absence of vitronectin (see page 13, lines 5-20, see also results in figure 2). Therefore, it would have been obvious to use PAI-1 as a thromlytic agent in an animal since it has been shown to inhibit thrombin in the absence and presence of virtronectin. It would have been further obvious, once formulating the pharmaceutical formulation, to provide instructions as to the mode of administration and dosage so the peptide could be used in a thrombolytic context.

6. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anish Gupta whose telephone number is (703) 308-4001. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback , can normally be reached on (703)306-3220. The fax phone number of this group is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Anish Gupta

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